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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/386,450	08/31/99	HOTTEN G	P564-9022

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EXAMINER	
ROMEO,D	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/386,450	Applicant Hotten et al.
	Examiner David Romeo	Group Art Unit 1647

☒ Responsive to communication(s) filed on *1 Sep 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *2-24* is/are pending in the application.

Of the above, claim(s) *2-4, 7, 10, 19, and 20* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *5, 6, 8, 9, 13, 15, 18, and 21-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *2-24* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *1*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 2-24 are pending.

2. Applicant's election with traverse of group I, claims 5, 6, 8, 9, 13, 15, 18, 21-24 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the claims of group II will have to be rejoined. This is not found persuasive because an application may properly be required to be restricted to one of two or more claimed invention if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (j)) or distinct (MPEP § 806.05 - § 806.05(i)). The Examiner has shown that the inventions of Groups I and II are distinct in the last Office action. Furthermore, M.P.E.P. § 803 provides that the separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a *prima facie* case that the search and examination of the plural inventions would impose a serious burden upon the Examiner; such separate classification was shown in the last Office action. Applicant has offered no evidence to rebut this showing. Furthermore, the withdrawn process claims do not depend from or otherwise include the limitations of a patentable product, and, thus, are not rejoined and are withdrawn from consideration. Applicants are reminded that group II, claims 16, 17, were subject to a species election requirement in the last Office action.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 2-4, 7, 10, 19, 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

4. Claims 5, 6, 8, 9, 13, 15, 18, 21-24 are being examined.

5. The computer readable form of the sequence listing filed 02/04/00 has been entered after correction of minor errors in the CRF by the Scientific and Technical Information Center staff. Specifically, the information for the 20th sequence was changed from "INFORMATION FOR SEQ ID NO: 21" to "INFORMATION FOR SEQ ID NO: 20".

6. The disclosure is objected to because of the following informalities:

a. the specification does not contain a brief description of drawings 3, 4, 5, 6.

b. the specification refers to "subject matter of claims 2 to 10". This reference is meaningless because the final claim number of the patent that it is to issue does not necessarily correspond to the original claim numbers. Furthermore, original claims 2-4, 7, 10 have been withdrawn from consideration and will not appear in the issued patent.

Appropriate correction is required.

7. The application is not fully in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See, for example, pages 15, 21. This is not meant to be an exhaustive list of places where the specification fails to comply with the sequence rules. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing."

Correction is required.

8. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 5, 6, 8, 9, 13, 15, 18, 21-24 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature. It is suggested that the claims be limited to an isolated polypeptide.

Claim Rejections - 35 USC § 112

11. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 6, 8, 9 are rejected under 35 U.S.C. § 112, second paragraph, since they depend from a canceled claim, and thus make no sense, since they are incomplete. In the interest of compact prosecution the claim will be interpreted as incorporating the limitations of the canceled

claim. However, this interpretation of the claim does not relieve applicant from the requirement to respond to the instant rejection.

The term "usual" in claims 8, 9 is a relative term which renders the claim indefinite. The term "usual" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 5, 6, 8, 9 are indefinite over the recitation of "functional parts thereof" because it is unclear what function associated with what part is intended. The metes and bounds of the claim(s) are not clearly set forth.

Claim(s) 8, 9, 15, 21, 22 are indefinite because they recite the term "auxiliary". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "auxiliary" an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term.

Claim(s) 5, 6, 8, 9, 13, 15, 18, 21-23 are indefinite because they recite the term "mature". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "mature" an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term.

Claim(s) 13, 15, 18, 21, 22 are indefinite over the recitation of "stringent conditions" because stringency varies according to the hybridization conditions and the particular hybrid under

study. Any degree of stringency is embraced by the claims. One of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 21, 22 are indefinite because it is unclear if the matrix is the carrier, substance, diluent, or filler, or if the composition comprises the matrix in addition to the carrier, substance, diluent, or filler. The metes and bounds of the claim(s) are not clearly set forth.

Claim 23 is indefinite over the recitation of "signal and/or propeptide parts" because it is unclear which "parts" are intended. The metes and bounds of the claim(s) are not clearly set forth. It is suggested that the claim recite "signal peptide or propeptide".

12. Claims 5, 6, 8, 9, 13, 15, 18, 21, 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification teaches a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1 that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2. SEQ ID NO: 1 and 2 meet the written description and enablement provision of 35 U.S.C. 112, first paragraph. However, the claims are directed to or encompass polypeptides encoded by polynucleotides that hybridize to SEQ ID NO: 1 and by allelic variants of SEQ ID NO: 1, which correspond to sequences from other species, mutated sequences, allelic variants, splice variants, and sequences that have some degree of identity

similarity, or homology. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar , 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGFs were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO:2 but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

13. Claims 5, 6, 8, 9, 13, 15, 18, 21, 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, does not reasonably provide enablement for a polypeptide encoded by a polynucleotide that hybridizes to SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The specification teaches a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1 that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2. SEQ ID NO: 1 and 2 meet the written description and enablement provision of 35 U.S.C. 112, first paragraph. However, the claims are directed to or encompass polypeptides encoded by polynucleotides that hybridize to SEQ ID NO: 1 and by allelic variants of SEQ ID NO: 1. However, the scope of the claims does not bear a reasonable correlation to the scope of the claims because the instant specification does not identify those amino acid residues in the amino acid sequence of an MP52 which are essential for its biological activity and structural integrity and those residues which are either expendable or

substitutable. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of over 100 amino acid residues before they could even begin to rationally design a functional MP52 having other than a natural amino acid sequence. The disclosure of a single DNA sequence encoding a single MP52 with a natural amino acid sequence is insufficient support under 35 U.S.C. § 112, first paragraph, for claims which encompass any and all MP52s, including mutants thereof, which are encoded by a DNA which hybridizes to a DNA having that single disclosed sequence. Furthermore, there is a lack of predictability in the art. Predicting structure, hence function, from primary amino acid sequence data is extremely complex and there doesn't exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. See Bowie (u7)[1] page 1306, column 1, full paragraph 1, and Ngo (v7) page 433, full paragraph 1, and page 492, full paragraph 2. Moreover, the specification teaches that there is a lack of predictability in the art with respect to TGF-β family members. The specification teaches "[o]n the whole these proteins show differences in their structure which leads to significant variations in their exact biological function" (page 2). Still

[1]References cited by the examiner are in an alphanumeric format, such as "a1", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

further, there are no functional limitations to the polypeptide and the specification has not told the skilled artisan how to use a polypeptide that does not induce endochondral bone formation.

The current claim limitations are directly analogous to those of claim 7 of U.S. Patent No. 4,703,008, which was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance a claim to a nucleic acid molecule encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. This limitation is directly analogous to the hybridization limitation of the instant claims. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes a DNA encoding an MP52, it does not describe even a single variant thereof. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify the grant of the patent protection sought in the instant claims. As indicated, the instant specification is even more limited than the '008 patent because it describes only a single protein and no analogs or mutants thereof

and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

14. Claims 8, 9, 15, 18, 21, 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a pharmaceutical composition for the induction of endochondral bone formation, does not reasonably provide enablement for a pharmaceutical composition, per se, or one used for the prevention or treatment of the tissues or conditions listed in claim 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The terms "pharmaceutical" and/or "pharmaceutically" encompass and/or imply preventing, diagnosing, alleviating, treating, or curing of a disease or condition in a mammal. The claims are directed to or encompass tissue regeneration. The claims encompass the regeneration of permanent cells that are retained throughout adult life and seem never to divide and which cannot be replaced if lost, such as almost all nerve cells, the muscle cells of the heart, the auditory

hair cells of the ear, and the lens cells of the eye. See Alberts(w7), pages 1142, last full paragraph, and pages 1144-1145. Although most permanent cells renew their parts, the claims encompass the growth of permanent cells, which cannot be replaced if lost. The specification fails to provide guidance for, or working examples of, regenerating permanent cells, which cannot be replaced if lost. The specification does not provide guidance for, or working examples of, "prevention". The claims encompass treating or preventing in adult tissues. Although the specification teaches GAG synthesis (page 24), the cells used were fetal cells. Fetal cells are undifferentiated and unlike the cells in an adult. As noted by Nathan (x7) many cytokines that subserve familiar functions postnatally play different or unknown roles embryologically and given the amino acid sequence of a cytokine and any of its actions one cannot predict when or where it will do what else (page 981, paragraph bridging columns 1-2). Accordingly, it appears that one skilled in the art would not extrapolate results with fetal tissues to those in a mammal. Although the specification teaches the maturation of an osteoblast cell line (page 26), MP52's effects were unlike those of BMP-2 in another osteoblast cell line, which is further evidence of the unpredictability in the art (paragraph bridging pages 27-28). The specification lacks guidance for, and working examples of, the regeneration of the tissues, other than bone, recited in claim 9 in the absence of bone formation such that the skilled artisan could reasonably expect that these tissues, other than bone, could be treated. Furthermore, claims 8, 9 appear to make the active ingredient optional and the specification lacks guidance for, and working examples of using a non-functional

pharmaceutical composition. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art, it would require undue experimentation for the skilled artisan to use the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

16. Claims 5, 6, 13, 15, 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee (1, cited by Applicants). This rejection is based upon an effective filing date of January 12, 1993 for mouse and human GDF-5s. Lee discloses an isolated polynucleotide encoding mouse GDF-5. Partial cDNA analysis of a human PCR product revealed no predicted amino acid differences between mouse and human GDF-5 (column 13, lines 23-25). Lee discloses that GDF-5 is a member of the TGF-β superfamily of proteins (paragraph bridging columns 2-3). Lee's mouse GDF-5 from nucleotides 1-2321 is 81.5% identical to nucleotides 325-2697 of Applicants' SEQ ID NO:1, as indicated below:

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  Query Match             56.9%;  Score 1537.2;  DB 4;  Length 2329;
  Best Local Similarity   81.5%;  Pred. No. 0;
  Matches 1942;  Conservative    0;  Mismatches  368;  Indels   74;  Gaps   11;

Qy    325 TTCAAGCCCTCAGTCAGTTGTGCAGGAGAAAGGGGGCGGTTGGCTTTCTCCTTTCAAGAA 384
          ||||||||||||||||||||||| |||||||||||||||| ||||||||||||||||||||
Db      1 TTCAAGCCCTCAGTCAGTTGTGCGGGAGAAAGGGGGCGGTCGGCTTTCTCCTTTCAAGAA 60

Qy    385 CGAGTTATTTTCAGCTGCTGACTGGAGACGGTGCACGTCTGGATACGAGAGCATTTCCAC 444
          |||||||||||||||||||||||||||||||||||||||||||| ||| ||||| ||||||
Db     61 CGAGTTATTTTCAGCTGCTGACTGGAGACGGTGCACGTCTGGACACGGGAGCACTTCCAC 120

Qy    445 TATGGGACTGGATACAAACACACACCCGGCAGACTTCAAGAGTCTCAGACTGAGGAGAAA 504
          |||||||||||||||| |||||| |||||| ||||||||||  ||||||||||||||||||
Db    121 TATGGGACTGGATACAGACACACGCCCGGCGGACTTCAAGACACTCAGACTGAGGAGAAA 180

Qy    505 GCCTTTCCTTCTGCTGCTACTGCTGCTG------CCGCTGCTTTTGAAAGTCCACTCCTT 558
          ||| | ||| |||||||| |||||||||      ||||||| | ||||   |||||||||
Db    181 GCCCTGCCTGCTGCTGCTGCTGCTGCTGCCACCGCTGCCTCTGAAGACCCACTCCTT 240

Qy    559 TCATGGTTTTTCCTGCCAAACCAGAGGCACCTTTGCTGCTGCCGCTGTTCTCTTTGGTGT 618
          |||||||||||||||||| |||||||||||| |||||| | ||  |||||| ||||||
Db    241 TCATGGTTTTTCCTGCCAAGCCAGAGGCACCTTCGCTGCTACGGCCTTTCTCTGTGGTGT 300

Qy    619 CATTCAGCGGCTGGCCAGAGGATGAGACTCCCCAAACTCCTCACTTTCTTGCTTTGGTAC 678
          |||||||||||||||||||||||||||||||||||||||||||| | ||||| ||| ||
Db    301 CATTCAGCGGCTGGCCAGAGGATGAGACTCCCCAAACTCCTCACTCTTTTGCTGTGGCAC 360

Qy    679 CTGGCTTGGCTGGACCTGGAATTCATCTGCACTGTGTTGGGTGCCCCTGACTTGGGCCAG 738
          |||||||||||||||||||| |||||||||||||| |||||||||||||||| || |||
Db    361 CTGGCTTGGCTGGACCTGGAACTCATCTGCACTGTGCTGGGTGCCCCTGACTTAGGACAG 420

Qy    739 AGACCCCAGGGGACCAGGCCAGGATTGGCCAAAGCAGAGGCCAAGGAGAGGCCCCCCCTG 798
          ||| |||  ||| ||| |||||| ||| ||||||| ||||||||||||||||| ||||||
Db    421 AGAACCCCAGGGGCCAAGCCAGGGTTGACCAAAGCGGAGGCCAAGGAGAGGCCACCCCTG 480

Qy    799 GCCCGGAACGTCTTCAGGCCAGGGGGTCACAGCTATGGTGGGGGGGCCACCAATGCCAAT 858
          ||| |||| ||||| |||||||||||||| | |||||||| ||||||||      |||||
Db    481 GCCAGGAATGTCTTTAGGCCAGGGGGTCATATCTATGGTGTGGGGGCCA------CCAAT 534

Qy    859 GCCAGGGCAAAGGGAGGCACCGGGCAGACAGGAGGCCTGACACAGCCCAAGAAGGATGAA 918
          |||||||| |||||| || | |||||             ||||||| ||||||||||||||
Db    535 GCCAGGGCCAAGGGAAGCTCTGGGCA------------GACACAGGCCAAGAAGGATGAA 582

Qy    919 CCCAAAAAGCTGCCCCCCAGACCGGGCGGCCCTGAACCCAAGCCAGGACACCCTCCCCAA 978
          |||| |||| |||||||||| | || ||| ||||| |||||||||| | || ||||
Db    583 CCCAGAAAGATGCCCCCCAGATCCGGTGGCTCTGAAACCAAGCCAGGACCCTCTTCCCAG 642

Qy    979 ACAAGGCAGGCTACAGCCCGGACTGTGACCCCAAAAGGACAGCTTCCCGGAGGCAAGGCA 1038
          || || |||||| |||||||||||| |||||||||||||||||||| || ||||| |||
Db    643 ACTAGACAGGCTGCAGCCCGGACTGTAACCCCAAAAGGACAGCTTCCTGGGGGCAAAGCA 702

Qy   1039 CCCCCAAAAGCAGGATCTGTCCCCAGCTCCTTCCTGCTGAAGAAGGCCAGGGAGCCCGGG 1098
            | |||||||||||||| |||||||||||||||||||||||| |||||||||| |||
Db    703 TCTTCAAAAGCAGGATCTGCCCCCAGCTCCTTCCTGCTGAAGAAGACCAGGGAGCCTGGG 762

Qy   1099 CCCCCACGAGAGCCCAAGGAGCCGTTTCGCCCACCCCCCATCACACCCCACGAGTACATG 1158
            |||| |||||||||||||||||| ||||| |||||||||||||||||||| ||||||
Db    763 ACCCCTCGAGAGCCCAAGGAGCCGTTCCGCCCGCCCCCCATCACACCCCACGAATACATG 822
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Qy   1159 CTCTCGCTGTACAGGACGCTGTCCGATGCTGACAGAAAGGGAGGCAACAGCAGCGTGAAG 1218
          ||||| ||||||||||||||||||||||||||||||||||||| |||||||||||||||
Db    823 CTCTCCCTGTACAGGACGCTGTCCGATGCTGACAGAAAGGGAGGTAACAGCAGCGTGAAG 882

Qy   1219 TTGGAGGCTGGCCTGGCCAACACCATCACCAGCTTTATTGACAAAGGGCAAGATGACCGA 1278
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    883 TTGGAGGCTGGCCTGGCCAACACCATCACCAGCTTTATTGACAAAGGGCAAGATGACCGA 942

Qy   1279 GGTCCCGTGGTCAGGAAGCAGAGGTACGTGTTTGACATTAGTGCCCTGGAGAAGGATGGG 1338
          || || | |||||||||||||||||||||||||||||| |||||| ||||||||||||||
Db    943 GGCCCTGCGGTCAGGAAGCAGAGGTACGTGTTTGACATCAGTGCCTTGGAGAAGGATGGG 1002

Qy   1339 CTGCTGGGGGCCGAGCTGCGGATCTTGCGGAAGAAGCCCTCGGACACGGCCAAGCCAGCG 1398
          ||| ||||||| || |||||||||||| |||||||||||| |||| ||||||||||||||
Db   1003 CTGTTGGGGGCTGAACTGCGGATCTTACGGAAGAAGCCCTTGGACGTGGCCAAGCCAGCG 1062

Qy   1399 GCCCCCGGAGGCGGGCGGGCTGCCCAGCTGAAGCTGTCCAGCTGCCCCAGCGGCCGGCAG 1458
          | |||| | |||||||||| |||||| ||||||||||||||||||||||||||||||||
Db   1063 GTCCCCAGTAGCGGGCGGGTTGCCCAACTGAAGCTGTCCAGCTGCCCCAGCGGCCGGCAG 1122

Qy   1459 CCGGCCTCCTTGCTGGATGTGCGCTCCGTGCCAGGCCTGGACGGATCTGGCTGGGAGGTG 1518
          |||||  ||||||||||||||||||||||||||||||||||| ||||||||||||||||||
Db   1123 CCGGCAGCCTTGCTGGATGTGCGCTCCGTGCCAGGCCTGGATGGATCTGGCTGGGAGGTG 1182

Qy   1519 TTCGACATCTGGAAGCTCTTCCGAAACTTTAAGAACTCGGCCCAGCTGTGCCTGGAGCTG 1578
          |||||||||||||||||||||||||| |||||||||| || ||||||||||||||||||
Db   1183 TTCGACATCTGGAAGCTCTTCCGAAATTTTAAGAACTCAGCGCAGCTGTGCCTGGAGCTG 1242

Qy   1579 GAGGCCTGGGAACGGGGCAGGGCCGTGGACCTCCGTGGCCTGGGCTTCGACCGCGCCGCC 1638
          |||||||||||||||| |||||||||||||||||||||||| || ||| | |||
Db   1243 GAGGCCTGGGAACGGGGCCGGGCCGTGGACCTCCGTGGCCTGGGCTTTGAACGCACTGCC 1302

Qy   1639 CGGCAGGTCCACGAGAAGGCCCTGTTCCTGGTGTTTGGCCGCACCAAGAAACGGGACCTG 1698
          || |||||||||||||| ||| ||||||| |||||||| || ||||||||||||||||||
Db   1303 CGACAGGTCCACGAGAAAGCCTTGTTCCTAGTGTTTGGTCGTACCAAGAAACGGGACCTG 1362

Qy   1699 TTCTTTAATGAGATTAAGGCCCGCTCTGGCCAGGACGATAAGACCGTGTATGAGTACCTG 1758
          |||||||||||||||||||||||||||||||||| || ||||| |||||||| ||  ||
Db   1363 TTCTTTAATGAGATTAAGGCCCGCTCTGGCCAGGATGACAAGACTGTGTATGAATATTTG 1422

Qy   1759 TTCAGCCAGCGGCGAAAACGGCGGGCCCCACTGGCCACTCGCCAGGGCAAGCGACCCAGC 1818
          |||||||||||||| ||||| |||||||| |||||| ||||||||||||||||||||||
Db   1423 TTCAGCCAGCGGCGGAAACGCCGGGCCCCATTGGCCAATCGCCAGGGCAAGCGACCCAGC 1482

Qy   1819 AAGAACCTTAAGGCTCGCTGCAGTCGGAAGGCACTGCATGTCAACTTCAAGGACATGGGC 1878
          |||||||| |||||||||||||||| |||||  ||||||||||||||||||||||||||
Db   1483 AAGAACCTCAAGGCTCGCTGCAGTCGCAAGGCCTTGCATGTCAACTTCAAGGACATGGGC 1542

Qy   1879 TGGGACGACTGGATCATCGCACCCCTTGAGTACGAGGCTTTCCACTGCGAGGGGCTGTGC 1938
          |||||||||||||||||||||| |||||||| ||||| |||||||||| || |||||
Db   1543 TGGGACGACTGGATCATCGCACCTCTTGAGTATGAGGCCTTCCACTGCGAAGGACTGTGT 1602

Qy   1939 GAGTTCCCATTGCGCTCCCACCTGGAGCCCACGAATCATGCAGTCATCCAGACCCTGATG 1998
          |||||||| |||||||||| ||||||||| || || |||||||| |||||||| |||
Db   1603 GAGTTCCCCTTGCGCTCCCACTTGGAGCCCACAAACCACGCAGTCATTCAGACCCTAATG 1662

Qy   1999 AACTCCATGGACCCCGAGTCCACACCACCCACCTGCTGTGTGCCCACGCGGCTGAGTCCC 2058
          ||||| |||||||| || |||||||||||||| || |||||||| || ||||||||||
Db   1663 AACTCTATGGACCCTGAATCCACACCACCCACTTGTTGTGTGCCTACACGGCTGAGTCCT 1722

Qy   2059 ATCAGCATCCTCTTCATTGACTCTGCCAACAACGTGGTGTATAAGCAGTATGAGGACATG 2118
          || |||||||||||||| |||||||||||||||||||||||||| ||||| |||||||||
Db   1723 ATTAGCATCCTCTTCATCGACTCTGCCAACAACGTGGTGTATAAACAGTACGAGGACATG 1782
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Qy   2119 GTCGTGGAGTCGTGTGGCTGCAGGTAGCAGCACTGGCCC-TCTGTCTTCCTGGGTGGCAC 2177
          |||||||| || ||||||||||||||||||||| |||||  ||||||||| |||||||||
Db   1783 GTCGTGGAATCTTGTGGCTGCAGGTAGCAGCACCGGCCCACCTGTCTTCCAGGGTGGCAC 1842

Qy   2178 ATCCCAAG---AGCCCCTTCCTGCACTCCTGGAATCACAGAGGGGTCAGGAAGCTG-TGG 2233
          ||||  ||   | |||||        ||||||| | |||||| |     ||||||| ||
Db   1843 ATCCAGAGACTACCCCCTCTACAGGTTCCTGGAGTAACAGAGAGCCTGTGAAGCTGCTGC 1902

Qy   2234 CAGGAGCATCTACACAGCTTGGGTGAAAGGGGATTCCAATAAGCTTGCTCGCTCTCTGAG 2293
          | | ||  ||    |||| ||   ||||| |   ||     |||  |||  |||||||
Db   1903 CCGAAGTTTCCTGGCAGCCTGCAGGAAAGAGTTCTC-----AGCAGGCTTACTCTCTGGA 1957

Qy   2294 TGTGACTTGGGCTAAAGGCCCCCTTTTATCCACAAGTTCCCCTGGCTGAGGATTGCTGCC 2353
          |||||  ||| ||||||    |   || |  |                       | | ||
Db   1958 TGTGATCTGGACTAAAGAGATCACCTTCTGAA----------------------GATTCC 1995

Qy   2354 CGTCTGCTGATGTGACCAGTGGCAGGCACAGGTCCAGGGAGACAGACTCTGAATGGGACT 2413
           | |    ||   |||     |  |||   || |   ||| |     ||| |||| || |
Db   1996 TGCCCAAGGAACAGACTCTGAGTGGGCCTGGGGCTCAGGAAAGGTGTTCTTAATGAGATT 2055

Qy   2414 GAGTCCCAGGAAACAGTGCTTTCCGATGAGACTCAGCCCACCATTTCTCCTCACCTGGGC 2473
           ||| |     | ||   ||       | | |  || ||  ||||||||  ||      |
Db   2056 CAGTTC-----ACCATCTCTCCTGCCGGGGCCGGAGACCTTCATTTCTCTCCAGACTCTC 2110

Qy   2474 CTTCTCAGCCTCTGGACTCTCCTAAGCACCTCTCAGGAGAGCCACAGGTGCCACTGCCTC 2533
          |     ||     |   | |||||||| | |    |||||         ||     ||||
Db   2111 CAGAGAAGTTGTAGCTATATCCTAAGCTCTTTAAGGGAGA---------GCTGTCTCCTC 2161

Qy   2534 CTCAAATCACATTTGTGCCTGGTGACTTCCTGTCCCTGGGACAGTTGAGAAGCTGACTGG 2593
          ||  |||||| ||||||||||||||||| ||| | |  |           ||  |   ||
Db   2162 CTTGAATCACCTTTGTGCCTGGTGACTTTCTGCCACGAGATGTTCATTACAGGGGCTGGG 2221

Qy   2594 GCAAGAGTGGGAGAGAAGAGGAGAGGGCTTGGATAGAGTTGAGGAGTGTGAGGCTGTTAG 2653
            ||||  |||| ||    ||   ||||  || |  ||   ||              ||||
Db   2222 CAAAGAAGGGGAAAG----GGCTTGGGCAGGGGTGAAGAGAAGAGTATGAGCCTAATTAG 2277

Qy   2654 ACTGTTAGATTTAAATGTATATTGATGAGATAAAAAGCAAAACT 2697
          |||||||||| |||||| || ||||| ||||||    || ||
Db   2278 ACTGTTAGATTAAAATGTACATCGATGACATAAAAGCTGAATCT 2321
```

The encoded polypeptide is greater than 90% identical to the instant SEQ ID NO: 2, as indicated below:

```
  Query Match           91.0%;  Score 3332;  DB 5;  Length 495;
  Best Local Similarity 91.2%;  Pred. No. 0.00e+00;
  Matches  457;  Conservative   23;  Mismatches  15;  Indels   6;  Gaps   2;

Db      1 MRLPKLLTLLLWHLAWLDLELICTVLGAPDLGQRTPGAKPGLTKAEAKERPPLARNVFRP 60
          ||||||||:||| |||||||:|||||||||||||  |::|||:||||||||||||||||||
Qy      1 MRLPKLLTFLLWYLAWLDLEFICTVLGAPDLGQRPQGTRPGLAKAEAKERPPLARNVFRP 60

Db     61 GGHIYGVGATNA--RAKGSSGQT----QAKKDEPRKMPPRSGGSETKPGPSSQTRQAAAR 114
          |||  || |||||  ||||::|||    |:|||||:|:|||:||:| |||  ::||||||:||
Qy     61 GGHSYGGGATNANARAKGGTGQTGGLTQPKKDEPKKLPPRPGGPEPKPGHPPQTRQATAR 120

Db    115 TVTPKGQLPGGKASSKAGSAPSSFLLKKTREPGTPREPKEPFRPPPITPHEYMLSLYRTL 174
          ||||||||||||||::||||| ||||||||:||||| ||||||||||||||||||||||||
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Qy    121 TVTPKGQLPGGKAPPKAGSVPSSFLLKKAREPGPPREPKEPFRPPPITPHEYMLSLYRTL 180

Db    175 SDADRKGGNSSVKLEAGLANTITSFIDKGQDDRGPAVRKQRYVFDISALEKDGLLGAELR 234
          ||||||||||||||||||||||||||||||||||| |||||||||||||||||||||||||
Qy    181 SDADRKGGNSSVKLEAGLANTITSFIDKGQDDRGPVVRKQRYVFDISALEKDGLLGAELR 240

Db    235 ILRKKPLDVAKPAVPSSGRVAQLKLSSCPSGRQPAALLDVRSVPGLDGSGWEVFDIWKLF 294
          |||||| | |||| |::|| ||||||||||||||:|||||||||||||||||||||||||
Qy    241 ILRKKPSDTAKPAAPGGGRAAQLKLSSCPSGRQPASLLDVRSVPGLDGSGWEVFDIWKLF 300

Db    295 RNFKNSAQLCLELEAWERGRAVDLRGLGFERTARQVHEKALFLVFGRTKKRDLFFNEIKA 354
          ||||||||||||||||||||||||||||:|:||||||||||||||||||||||||||||||
Qy    301 RNFKNSAQLCLELEAWERGRAVDLRGLGFDRAARQVHEKALFLVFGRTKKRDLFFNEIKA 360

Db    355 RSGQDDKTVYEYLFSQRRKRRAPLANRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIA 414
          |||||||||||||||||||||||| |||||||||||||||||||||||||||||||||||||
Qy    361 RSGQDDKTVYEYLFSQRRKRRAPLATRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIA 420

Db    415 PLEYEAFHCEGLCEFPLRSHLEPTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFID 474
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    421 PLEYEAFHCEGLCEFPLRSHLEPTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFID 480

Db    475 SANNVVYKQYEDMVVESCGCR 495
          |||||||||||||||||||||
Qy    481 SANNVVYKQYEDMVVESCGCR 501
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The specification fails to precisely define "stringent conditions". Lee's polynucleotide would hybridize to SEQ ID NO:1, absent evidence to the contrary. Lee et al. also teach vectors comprising GDF-5 polynucleotide sequences (paragraph bridging columns 6-7), bacterial host cells comprising said vectors, as recited in claims 18 and 19 (column 7, full paragraphs 1-3), and a process for producing GDF-5 polypeptide, as recited in claim 22 (column 7, full paragraph 1). There are no structural limitations to the "dental implant" of claim 18. GDF-5 is a dental implant, absent evidence to the contrary.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 5, 6, 8, 9, 13, 15, 18, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (1, cited by Applicants) as applied to claims 5, 6, 13, 15, 18 above. Lee discloses mouse and human GDF-5, as discussed above. Lee is silent with respect to a pharmaceutical composition comprising GDF-5. Lee also teaches that it can be expected that GDF-5 will be useful as a diagnostic and therapeutic agent (paragraph bridging columns 2-3). It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a pharmaceutical composition comprising GDF-5, as taught by Lee, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make a pharmaceutical composition in order to study GDF-5 as a diagnostic and therapeutic agent. The invention is prima facie obvious over the prior art.

Conclusion

19. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Romeo
Primary Examiner
November 19, 2000